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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/731,255	12/06/2000	Joel E. Habener	14875-115US1/C1-108PCT-US	9070

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/731,255	HABENER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspond nce address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-127* is/are pending in the application.

4a) Of the above claim(s) *1-24,36-66 and 80-127* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-35 and 67-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-127* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 04 April 2003 has been entered in full. Claims 25-26, 68-69, and 72 are amended.

This application contains claims 1-24, 36-66, and 80-127 drawn to an invention nonelected without traverse in the Paper of 23 September 2002. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 25-35 and 67-79 are under consideration in the instant application.

Sequence Compliance

1. The Applicant's response to the Notice to Comply with Sequence Listing Requirements under 37 CFR §1.821 04 April 2003 has been considered and is found persuasive. Therefore, the requirements set forth in the Notice to Comply of 04 December 2002 are withdrawn.

Withdrawn Objections and/or Rejections

2. The objections to the specification at pg 2-3 of the previous Office Action (04 December 2002) are *withdrawn* in view of the amended specification and title (04 April 2003).

3. The objection to claims 25-26 and 68-69 at pg 3-4 of the previous Office Action (04 December 2002) is *withdrawn* in view of the amended claims (04 April 2003).

4. The rejections of claims 25-35, 72, and 79 under 35 U.S.C. § 112, second paragraph, as set forth at pg 7-8 of the previous Office Action (04 December 2002) are *withdrawn* in view of the amended claims (04 April 2003).

5. The rejection of claims 25-35 and 67-79 under 35 U.S.C § 112, first paragraph, as set forth at pg 4-7 of the previous Office Action (04 December 2002) is *withdrawn in part* in view of the evidence submitted with Applicant's responses of 04 April 2003 and 27 May 2003. Please see section below on 35 U.S.C. § 112, first paragraph, scope of enablement.

Claim Rejections - 35 USC § 112

6. Claims 25-35 and 67-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a non-human subject or human subject with diabetes mellitus, comprising the steps of (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a human donor; (b) expanding the stem cell to produce a progenitor cell, (c) differentiating the progenitor cell in culture to form pseudo-islet like aggregates; and (d) transferring the pseudo-islet like aggregates into the non-human or human subject, does not reasonably provide enablement for a method of treating a patient with diabetes mellitus, comprising the steps of: (a) isolating the nestin-positive pancreatic stem cell from a pancreatic islet of a donor; (b) expanding the stem cell to produce a progenitor cell, (c) differentiating the progenitor cell in culture to form pseudo-islet like aggregates; and (d) transferring the pseudo-islet like aggregates into the patient. Additionally, the specification, while being enabling for a method of transplanting pseudo-islet like aggregates into a non-human mammal or human, comprising the steps of: (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a human donor; (b) expanding the stem cell to produce a progenitor

cell; (c) differentiating the progenitor cell in culture to form pseudo-islet like aggregates; and (d) transferring the pseudo-islet like aggregates into the non-human mammal or human, does not reasonably provide enablement for a method of transplanting into a mammal, comprising the steps of: (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor; (b) expanding the stem cell to produce a progenitor cell; (c) differentiating the progenitor cell in culture to form pseudo-islet like aggregates; and (d) transferring the pseudo-islet like aggregates into the mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, claims 25-35 and 67-69 are directed to a method of treating a patient with diabetes mellitus or a method of transplanting into a mammal, comprising the steps of: (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet, (b) expanding the stem cell to produce a progenitor cell, (c) differentiating the progenitor cell in culture to form pseudo-islet like aggregates, and (d) transferring the pseudo-islet like aggregates into the patient, wherein the patient does not serve as the donor for the stem cells and wherein said transferring step (d) treats diabetes mellitus. The claims also recite that the donor is a patient/mammal is a human and the donor is a non-human mammal. The claims recite that the patient/mammal is not treated with an immunosuppressive agent prior to step (b). The claims also recite that the step of expanding is performed in the presence of an agent and the step of transferring is performed via endoscopic retrograde injection. The claims recite that the method additionally comprises treating the patient with an immunosuppressive agent.

Applicant's arguments (04 April 2003 and 27 May 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the specification teaches how to isolate nestin-positive pancreatic stem cells from a donor (pg 42-43), how to expand the stem cells to produce progenitor cells (pg 43-44), how to transfer the pseudo-islet like progenitors into a patient (pg 38-39, Examples 8-10). Applicant argues that there is post-filing date literature teaching treatment of diabetic SCID mice by implantation of human derived nestin positive stem cell aggregates that resemble islets (NPAs; Exhibit A; Wu et al.; from meeting "Pancreatic Development, proliferation, and stem cells", 2001). Applicant also asserts that a second post-filing date abstract (Wu et al.; Exhibit B; from U.C. Davis/VSTP Retreat, August 26, 2002) discloses that human NPAs implanted into streptozotocin induced diabetic mice were able to maintain essentially normal glucose concentrations, without exogenous insulin, for more than 70 days, and exhibited essentially normal glucose tolerance tests. Applicant states that the data presented in the abstracts demonstrate the treatment of diabetes mellitus by the transfer of pseudo-islet aggregates into a patient. Applicant indicates that in view of the teachings of the specification, and in further view of the abstracts, one of skill in the art would have no reason to predict that graft or transplant rejection would occur if a human patient were transplanted with pseudo-islet like aggregates.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as discussed in the previous Office Action of 04 December 2002, the state of the art is such that patients may suffer one of two types of graft or transplant rejections, host-versus-graft rejection or graft-versus-host rejection (GvHR). In host-versus-graft rejection, the patient's immune cells have an immune response to the graft's antigens while in GvHR, the graft rejects

the patient's tissues. Since claims 25 and 67 recite that the patient/mammal does not serve as the donor for the nestin-positive pancreatic stem cells, the skilled artisan cannot predict that the differentiated pseudo-islet like aggregates can be successfully immunologically transplanted into the recipient patient/mammal. Furthermore, the specification of the instant application and the claims do not disclose the identity of the nestin-positive pancreatic stem cell donor. For example, the cells could be from another human, a pig, monkey, rat, etc. and therefore possibly cause host-versus-graft rejection or GvHR in the recipient patient.

Furthermore, the abstracts submitted by Applicant as Exhibits A and B teach the implantation of *human* nestin positive cells (NPCs) derived from the pancreas into streptozotocin induced diabetic mice and diabetic SCID mice. These abstracts do not teach the implantation of *non-human* pseudo-islet like aggregates into a *human*. Therefore, the disclosure in the instant application and the post-filing date references are still not adequate guidance, but merely an invitation for the artisan to use the current invention as a starting point for further experimentation. Additionally, one skilled in the art would not be able to predict the successful transplantation of the pseudo-islet like aggregates into any patient simply based upon the results with the mice utilized in the experiments of Exhibits A and B. For instance, diabetes mellitus is induced in the mice of Exhibit A by the toxin, streptozotocin. Streptozotocin induces diabetes through its toxic effect on pancreatic beta cells and evidence for autoimmune involvement is lacking (Szkudelski, T., Physiol Rev 50: 536-546, 2001; pg 541. ¶ 4-6). Also, Exhibit B utilizes diabetic SCID (severe combined immunodeficiency) mice. SCID mice have a mutation that prevents lymphocyte differentiation. These mice have normal microenvironments for B and T cell differentiation from stem cells, so grafting normal bone marrow into SCID mice can

generate an intact immune system (Janeway and Travers. *Immunobiology*. London: Current Biology Limited, 1997; pg 2:46, section 2-33). However, since these mice are immunodeficient, one skilled in the art cannot predict the successful implantation of pseudo-islet like aggregates into a patient, as the patient may experience host-versus-graft rejection or graft-versus-host rejection.

It is noted that relevant literature also indicates that there are still several barriers to islet transplantation as a treatment for diabetes. For example, Soria et al. (Diabetologia 44: 407-415, 2001) indicate that such barriers to this treatment approach include: immunological rejection, the diabetogenic effects of some immunosuppressant agents, the oncogenic effects of long-term immunosuppressive treatment, and insufficient number of cells transplanted (pg 407, col 2).

(ii) Applicant argues that absolute predictability is not required, the claims may encompass some inoperative species, and some experimentation is permitted.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that it is not a function of the claims to specifically exclude possible inoperative embodiments, and the presence of inoperative embodiments within the scope of a claim does not preclude enablement of the claim. However, the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. MPEP § 2164.08(b) states that "claims reading on significant numbers of inoperative embodiments would render the claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.

(iii) Applicant asserts in the supplemental response of 27 May 2003 that there is post-filing date literature teaching treatment of diabetic NOD-SCID mice by implantation of islet-like cell clusters (ICCs) derived from cultured human fetal nestin-positive-islet-derived progenitor cells (Huang et al., Lab Invest 83(4): 539-547, 2003). Applicant contends that this publication demonstrates the actual reduction to practice of the invention of the instant application. Applicant states that the data presented in Huang et al. demonstrate the treatment of diabetes mellitus by the transfer of ICCs into a patient. Applicant submits that this exhibit demonstrates the transplanted pseudo-islet like aggregates (ICCs) act like healthy islet cells and effect blood glucose levels, resulting in reversal of hyperglycemia, indicative of diabetes treatment.

Applicant's arguments have been fully considered but are not found to be persuasive. As mentioned above, the state of the art is such that patients may suffer one of two types of graft or transplant rejections, host-versus-graft rejection or graft-versus-host rejection (GvHR). In host-versus-graft rejection, the patient's immune cells have an immune response to the graft's antigens while in GvHR, the graft rejects the patient's tissues. Since claims 25 and 67 recite that the patient/mammal does not serve as the donor for the nestin-positive pancreatic stem cells, the skilled artisan cannot predict that the differentiated pseudo-islet like aggregates can be successfully immunologically transplanted into the recipient patient/mammal. Furthermore, the specification of the instant application and the claims do not disclose the identity of the nestin-positive pancreatic stem cell donor. For example, the cells could be from another human, a pig, monkey, rat, etc. and therefore possibly cause host-versus-graft rejection or GvHR in the recipient patient.

Similar to the Wu et al. abstracts of Exhibits A and B, one skilled in the art would not be able to predict the successful transplantation of the pseudo-islet like aggregates into any patient simply based upon the results with the mice utilized in the experiments of Huang et al. Huang et al. teach the implantation of human islet-like cell clusters (ICCs) into streptozotocin-induced diabetic NOD-SCID mice (pg 542, 3rd full ¶; pg 543, first full ¶; pg 546). NOD-SCID mice are a mouse strain developed by crossing SCID mice with nonobese diabetic mice. Therefore, the mice utilized in Huang et al. are immunodeficient, spontaneously develop diabetes mellitus, and have diabetes induced by streptozotocin. These mice are also administered human ICCs. One skilled in the art would not be able to predict the successful implantation of pseudo-islet like aggregates (ICCs) from any donor into any patient (particularly human), as the patient may experience host-versus-graft rejection or graft-versus-host rejection. Also, Huang et al. does not teach the implantation of *non-human* pseudo-islet like aggregates into a *human*.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to transfer pseudo-islet like aggregates into any patient (particularly human) from any donor and treat diabetes, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the art (see discussion above), and the unpredictability of the activity and immunologic effects of the pseudo-islet like aggregates once administered to the patient, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Double Patenting

7. The rejection of claims 25, 38-30, and 35 under the judicially created doctrine of obviousness-type double patenting as set forth at pg 8-9 of the previous Office Action (04 December 2002) is maintained and held in abeyance until all other issues are resolved. However, Applicant is encouraged to submit a terminal disclaimer at Applicant's earliest convenience.

8. The rejection of claims 67-68, 72-74, and 79 under the judicially created doctrine of obviousness-type double patenting as set forth at pg 9-10 of the previous Office Action (04 December 2002) is maintained and held in abeyance until all other issues are resolved. However, Applicant is encouraged to submit a terminal disclaimer at Applicant's earliest convenience.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Atkinson et al. Nat Med 5(6) : 601-604, 1999.
van der Loo et al. Blood 92 (7) : 2556-2570, 1998.
Yoon et al. Ann NY Acad Sci 928: 200-211, 2001.
Greiner et al. Stem Cells 16 : 166-177, 1998.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
12 November 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER